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Review/ Praca poglądowa

Efficacy and safety of bosutinib in the second and third line of treatment in chronic myeloid leukemia

Skuteczność i bezpieczeństwo bozutynibu w leczeniu drugiej i trzeciej linii linii przewlekłej białaczki szpikowej

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ABSTRACT

Tyrosine kinases inhibitors (TKIs) are the mainstay of chronic myeloid leukemia (CML) treatment. The choice of a specific TKI depends on its side effects, disease phase, ABL mutations, concomitant diseases, and reimbursement possibility. Bosutinib is a second generation TKI (2GTKI) approved for the treatment of patients with CML in all phases, previously treated with ≥1 TKI, who cannot be treated with imatinib, nilotinib or dasatinib. It is active against the majority of mutant BCR-ABL1, except T315I and V299L. Response rates in patients resistant or intolerant to imatinib treated with bosutinib are similar to those observed for other 2GTKI. Bosutinib may be also effective in patients with advanced phases of CML after other TKI failure. The most common side effects include gastrointestinal symptoms, rash, and increased transaminase activity. Bosutinib causes less cases of pleural effusion, hypercholesterolemia, hyperglycemia, and cardiovascular complications than other TKIs, therefore it is a very important therapeutic option for patients with these disorders.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that comprises approx. 10% leukemia cases in adults. CML is characterized by the presence of reciprocal translocation between the long arms of chromosomes 9 and 22, which leads to the formation of Philadelphia chromosome (Ph, shortened chromosome 22), that results in expression of fusion oncogene BCR-ABL1 consisting of BCR located on chromosome 22 and ABL1 gene derived from chromosome 9 [1–3]. BCR-ABL1 encodes a protein kinase Bcr-Abl that is responsible for the impairment of regulatory processes in the cell, including cell cycle and DNA repair

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regulation [1, 3–6]. This leads to increased proliferation rate and reduced apoptosis of myeloid cells.

The majority of CML cases are diagnosed in the chronic phase (CP) that may progress to accelerated phase (AP) and subsequent blast phase (BP) or directly to BP (tri- or biphasic course of the disease, respectively).

Introduction of tyrosine kinases inhibitors (TKIs) significantly improved the prognosis of CML patients and has become a paradigm of effective targeted therapy [7, 8]. Imatinib was the first TKI used in the treatment of CML [9, 10]. Dasatinib and nilotinib are second generation TKIs (TKI2G) [11–14]. Despite the effectiveness and long-term safety of imatinib, approx. 40% of patients require switch to other TKIs due to the development of resistance or intolerance [15, 16]. Approx. half of them achieve complete cytogenetic response (CCyR) when treated with TKI2G [17, 18]. In addition, TKI2G in first line of CML-CP treatment allow to achieve deep molecular responses faster and in a larger number of patients, however, they do not improve overall survival in this group [19, 20]. The choice of a specific TKI for the treatment of CML depends on its side effects profile, disease phase, ABL kinase domain mutations, concomitant diseases, as well as the costs and the possibility of treatment reimbursement [21, 22].

Bosutinib (SKI-606) is another TKI2G that inhibits both Bcr-Abl and Src family of kinases. Bosutinib was approved by the European Medicines Agency in 2013 for the treatment of adult patients with CML in all phases, who were previously treated with one or more TKI, who cannot be treated with imatinib, nilotinib or dasatinib [23]. The aim of this paper is to provide pharmacological data regarding efficacy and toxicity of bosutinib in the treatment of CML (on-label use).

Pharmacodynamics

Bosutinib (SKI-606) was identified in 2001 by Boschelli as a potent inhibitor of non-receptor, protein Src kinases involved in various signaling pathways, including surface receptor and Bcr-Abl kinase pathways [24–26]. The Src family kinases are involved in malignant transformation, tumor progression, and formation of metastases [25]. It is believed that these interactions are responsible for the progression of CML to AP and BP [25, 27]. Active sites of Src and c-Abl kinases are structurally related [28–30]. In 2003, Golas et al. showed that bosutinib (1–20 nmol/l) exerts more potent antiproliferative and proapoptotic efficacy in CML cell lines (K562, KU812, Meg-01) than imatinib [30]. Moreover, in murine and human myeloid cells bosutinib was active against imatinib-resistant, mutated forms of Bcr-Abl (Y253F, E255K, and D276G) [25, 31]. No activity in patients with T315I and V299L mutations was observed [25, 27, 29, 31–33]. Bosutinib also inhibits a number of other kinases involved in the promotion stage of carcinogenesis in myeloid leukemia cells. These include thyrosine kinases, serine-threonine kinases, and two calmodulin-dependent protein kinases [32, 34]. Unlike other TKIs, bosutinib is only minimally active against c-Kit and platelet-derived growth factor receptor (PDGFR), which play a role in normal hematopoiesis [24, 25, 34, 35]. Activity profile of bosutinib may explain its relatively low myelosuppressive potential in comparison to other TKIs [35]. Further studies performed by Konig et al. showed that bosutinib does not exert any significant effect on quiescent progenitor CML cells [36].

Pharmacokinetics

The pharmacokinetic parameters of bosutinib do not depend on age, weight, gender or ethnicity. The absorption of the oral forms of bosutinib from the gastrointestinal tract is slow, dose-dependent, and might be influenced by simultaneous consumption of food, and a pH of gastric acid [37, 38]. In phase I clinical trials, median maximal serum concentration (C_{max}) was achieved 4–6 h after the administration of a single dose of the drug. Area under the curve (AUC) (serum concentration to time) after oral administration of bosutinib was 1.6–1.7 times higher if the drug was administered with food compared to the administration on an empty stomach [37, 38]. Bosutinib administered with food (200–600 mg) was safe and well tolerated, while doses greater than 400 mg administered on an empty stomach were associated with increased risk of adverse events, including diarrhea and nausea. At 400 mg/day diarrhea was observed in 83% of patients who took the drug on an empty stomach and 33% of patients who took the drug during a meal [38]. Simultaneous food intake increase the solubility of bosutinib and increase the absorption and tolerance of the drug. Volume of distribution of bosutinib is 5000–7000 L, what translates into a significant penetration and accumulation of the drug in the tissues. The absorption of bosutinib is lower if pH of gastric acid exceeds 5. Therefore, patients requiring antacid treatment should use short-acting H_2-blockers instead of proton pump inhibitors. H_2-blockers should be administered at least 2 h apart from bosutinib [23].

Bosutinib binds strongly (96%) to plasma proteins. It inhibits glycoprotein P (Pgp) and is metabolized in liver to inactive metabolites by cytochrome P450 isoenzyme 3A4 (CYP3A4) with “first pass effect” [39, 40]. Simultaneous administration of CYP3A4 inhibitors, such as ketoconazole or grapefruit juice, as well as inducers (e.g. rifampicin) may increase or decrease plasma concentration of bosutinib, respectively [40, 41]. In addition, simultaneous administration of Pgp inhibitors may increase plasma concentrations of bosutinib [23]. Such drug combinations should be avoided.

Bosutinib is contraindicated in patients with liver failure because of 2-fold increase of AUC and C_{max} of the drug in this group [23, 39]. Moderate (creatinine clearance 30–50 ml/min/1.73 m^2) or severe (creatinine clearance <30 ml/min/1.73 m^2) renal failure leads to 35% or 60% increase in AUC, respectively, in comparison to patients with normal kidney function [23]. In patients with renal failure bosutinib dose should be reduced. Elimination half-life of bosutinib is 22.5 h and in consequence, the drug is administered once daily [23, 37, 38]. Approx. 91% of inactive metabolites of bosutinib is excreted in faeces [23, 39].

Clinical trials of bosutinib – results

Study evaluating SKI-606 (bosutinib) in Philadelphia Chromosome Positive Leukemias (NCT00261846) was an open,

multicenter, I/II phase clinical trial evaluating efficacy, safety and pharmacokinetics of bosutinib in CML-CP, AP and BP patients resistant or intolerant to imatinib. The results of these trials are shown below, including the efficacy of the second-line, third-line and subsequent lines of treatment in chronic phase as well as AP and BP.

Primary TKI resistance was defined as lack of hematologic response after 4 weeks of treatment, lack of complete hematologic response (CHR) after 12 weeks, lack of any cytogenetic response after 24 weeks or lack of major cytogenetic response (MCyR) after 12 months [35, 42]. Acquired resistance was defined as a loss of any hematologic response or MCyR [35, 42]. TKI intolerance was defined as the inability to continue the treatment due to 4 grade hematologic toxicity for longer than 7 days, non-hematologic toxicity grade ≥3, persistent grade 2 toxicity that do not respond to dose reduction or symptomatic treatment, loss of response to low dose TKI treatment if dose increase is not possible due to TKI toxicity [35, 42]. In total 17 patients in CP and 1 patient in AP were enrolled to phase 1 trial. Clinical benefits have been observed at all administered doses (400, 500, and 600 mg/day). Because of two cases of dose-limiting toxicity (DLT) observed in a cohort receiving 600 mg of bosutinb (3 grade diarrhea and vomiting, and increased ALT) and the absence of such side effects in other cohorts, the phase II study was performed using 500 mg, with the possibility to increase the dose up to 600 mg in patients without grade 3/4 toxicity who do not achieve CHR after 8 weeks or CCyR after 12 weeks [35].

The efficacy of II line treatment with bosutinib

The population of patients receiving bosutinib in II line included 288 patients with CML-AP, among whom 200 were resistant and 88 were intolerant to imatinib. The median follow-up was 24.2 months. The median administered dose was 485 mg/day in patients resistant to imatinib and 394 mg/day in patients intolerant of imatinib. The results are shown in Table I. The effectiveness of bosutinib was similar in patients resistant and intolerant to imatinib, with the exception of complete molecular response rates (CMR), which were higher in patients intolerant to imatinib (61% vs. 49%). Response rates in patients with an identified mutation of the *BCR-ABL1* at baseline ($n = 115$) and in patients without any mutation were similar, with the exception of T315I mutation which is insensitive to bosutinib. After 4 years of follow-up, progression to AP or BP was observed in 4% of patients on bosutinib.

In 2014 Gambacorti-Passerini et al. presented the results of 2-years observation in this study [44]. The median follow-up was 30.5 months (0.6–66.0) for patients resistant to imatinib and 35.1 months (0.7–58.0) for patients intolerant to imatinib. The results (Table I) were similar to the results achieved with other second generation TKI in the second line of treatment [17, 18]. The median time to achieve MCyR was approx. 12 weeks in both groups of patients. In turn, median time to achieve MMR was 35.9 weeks in patients resistant to imatinib and 12.2 weeks in patients intolerant to imatinib.

The results of the study obtained after median 43.6 months of follow-up confirmed the long-term effectiveness of bosutinib in this group (Table I) [44].

In the majority of cases response was achieved within the first 2 years of treatment [43], and 4-year probability of maintaining MCyR or CCyR was 75% and 76%, respectively [44]. No new cases of progression to AP or BP were observed. Younger age (<65 years), male sex, any cytogenetic response to imatinib in the past, initial MCyR, interferon treatment in the past, less than 6 months from the diagnosis to the initiation of imatinib treatment are additional favorable prognostic factors for maintaining or achievement of MCyR or CCyR. Bosutinib treatment was temporarily ceased at various stages of the therapy in 60% of patients. 2-Year overall survival was 91% in general population and 88% and 98% in patients resistant or intolerant to imatinib, respectively. After 4 years of follow-up progression or death was reported in 19% of patients. In the course of the trial 40 deaths were observed (14%). The majority of cases were caused by disease progression or adverse events not related to the therapy. None of the deaths was caused by administration of bosutinib.

The efficacy of III line treatment with bosutinib

Khoury et al. evaluated the safety and efficacy of bosutinib in the third line treatment of CML-CP in 118 patients

Table I – The results of I/II phase trial of bosutinib in the treatment of chronic phase chronic myeloid leukemia patients resistant or intolerant to imatinib [35, 43, 44]

	Median duration of follow-up			
	24 weeks [35]	24.2 months [35]	30.5[c]/35.1[d] months [43]	43.6 months [44]
CHR	86%	86%	85%	85%
MCyR	31%[a]	53%	59%	59%
CCyR	23%	41%	48%	49%
MMR[b]	No data	64%	35%	No data
CMR[b]	No data	53%	28%	No data

CCyR – complete cytogenetic response, CHR – complete hematologic response, CMR – complete molecular response, MCyR – major cytogenetic response, MMR – major molecular response.
[a] Primary objective.
[b] Percentage of molecular response applies only to patients with CCyR.
[c] Patients resistant to imatinib.
[d] Patients intolerant to imatinib.

Table II – The results of I/II phase trial of bosutinib in the treatment of chronic phase chronic myeloid leukemia patients resistant or intolerant to imatinib after failure of ≥2 TKIs [35, 43, 44]

	Total	Imatinib + intolerance to dasatinib	Imatinib + resistance to dasatinib	Imatinib + resistance to nilotinib	Imatinib + dasatinib + nilotinib + (*n* = 3) or imatinib + intolerance to nilotinib (*n* = 1)
Number of patients	118	50	38	27	4
CHR	73%	62%	80%	77%	75%
MCyR	32%	31%	30%	35%	50%
CCyR	24%	14%	28%	27%	50%
MMR[a]	15%	1%	25%	8%	0
CMR[a]	11%	0	19%	8%	0

CCyR – complete cytogenetic response, CHR – complete hematologic response, CMR – complete molecular response, MCyR – major cytogenetic response, MMR – major molecular response.
[a] Percentage of molecular response applies only to patients with CCyR.

resistant or intolerant to other TKIs [42]. The patients were treated with imatinib in the first line, and with dasatinib or nilotinib in the second line. The median follow-up was 28.5 months (range 0.3–56.2). Treatment outcomes in each group are shown in Table II. In the course of the treatment 19% of patients (*n* = 20) needed bosutinib dose escalation from 500 to 600 mg due to lack of efficacy (i.e. no CHR after 8 weeks or CCyR after 12 weeks). This result was similar to previous observations (Cortes et al.) (18%) [35]. After dose escalation, the treatment response was observed in 30% patients (*n* = 6). Noteworthy, bosutinib treatment led to CCyR in 1 out of 3 patients who previously failed to respond to all three TKIs. Only in 4% of patients (*n* = 5) progression to AP was observed. No progressions to blast phase were observed.

Thirty-nine patients with BCR-ABL1 kinase domain mutations were enrolled to the study. CHR and MCyR were observed in patients with F317L (dasatinib resistant) as well as Y253H, E255K/V, and F359C/I/V mutations (nilotinib resistant). In the course of the trial, in 9 patients, the emergence of new mutations was observed (usually V299L). The treatment was discontinued in 8 of them, due to disease progression or unsatisfactory response. The efficacy of bosutinib in patients with T315I mutations (*n* = 7) was low – CHR was achieved in 2 patients and MCyR in 1 patient. One-year progression free survival (PFS) and overall survival were 77% and 91%, respectively [42].

The results of this study with median follow-up of 32.7 months (0.3–93.3) were published in 2016. In this dataset, CHR and MCyR were 74% and 40%, respectively. Four-year OS calculated using Kaplan-Mayer curve was 78% [45]. The results of this study confirmed long-term efficacy of bosutinib in patients with CML-CP resistant or intolerant to ≥2 TKIs.

The efficacy of bosutinib in accelerated phase and blast crisis

The efficacy of bosutinib in CML-AP (*n* = 63), CML-BP (*n* = 48), and Philadelphia-positive acute lymphoblastic leukemia (Ph + ALL, *n* = 23) was assessed by Gambacorti-Passerini et al. with median follow-up 8.3 months. The study enrolled imatinib-resistant or intolerant patients who received bosutinib in a daily dose of 500 mg [46]. After imatinib the patients were treated with interferon (*n* = 43), dasatinib (*n* = 45), nilotinib (*n* = 16) or allogenic hematopoietic stem cell transplantation (*n* = 12). Response to bosutinib is shown in Table III. Median PFS calculated using Kaplan–Meier curve was 11.6 months. Forty out of 66 participants had *BCR-ABL1* mutations other than T315I. Response to bosutinib was similar in patients with the above-mentioned mutations (CHR: 50%, MCyR: 47%), and without these mutations (CHR: 47%, MCyR: 54%). Nine of 10 patients with T315I mutation were resistant to bosutinib. The results of long-term observation of bosutinib treatment in advanced stages of CML were published in 2015. Four years after enrollment of the last patient, 14/79 CML-AP and 2/64 CML-BP patients remained on bosutinib treatment (mean treatment duration 10.2 months for AP and 2.8 months for BP) (Table IV) [47]. Treatment response was durable in approx. 50% of patients with AP. Due to the short response in patients with BP (approx. 25% after one year of treatment) bosutinib can be used in this group of patients as a bridge to transplantation of hematopoietic stem cells. Response rates were significantly higher in patients previously treated with imatinib only, compared to patients treated with other TKIs.

Table III – The results of I/II phase trial of bosutinib in the treatment of accelerated phase and blast phase CML patients resistant or intolerant to imatinib [46]

	Accelerated phase	Blast phase
CHR	61%	32%
CCyR	33%	29%
MCyR	40%	37%
MMR[a]	15%	28%

CCyR – complete cytogenetic response, CHR – complete hematologic response, MCyR – major cytogenetic response, MMR – major molecular response.
[a] Percentage of molecular response applies only to patients with CCyR.

Toxicity of bosutinib

Bosutinib is well-tolerated. Its toxicity profile demonstrated in clinical trials differs from other TKIs [35, 42]. The most commonly observed adverse effect is gastrointestinal toxicity (diarrhea, nausea, and vomiting), while pleural effusion,

Table IV – The results of I/II phase trial of bosutinib in the treatment of accelerated phase and blast phase chronic myeloid leukemia patients resistant or intolerant to imatinib – 4 year follow-up [47]

	Accelerated phase			Blast phase		
	Total	2. line	≥3. line	Total	2. line	≥3. line
Number of patients	72	43	29	60	34	26
OHR	57%	67%	41%	28%	38%	15%
4-Year likelihood of maintaining OHR		49%			19%	
MCyR	40%	48%	27%	37%	50%	21%
4-Year likelihood of maintaining MCyR		49%			21%	

MCyR – major cytogenetic response; OHR – overall hematologic response rate.

Table V – Adverse effects of bosutinib observed in the "Study evaluating SKI-606 in Philadelphia Chromosome Positive Leukemias" after minimum 4 years of follow-up in II line of treatment or 3 years in III line of treatment or AP/BP treatment [48]

Adverse effect	All grades	Grade 3 and 4
Diarrhea	82%	8%
Nausea	47%	1%
Vomiting	39%	3%
Thrombocytopenia	42%	30%
Rash	33%	6%
Fever	27%	1%
Anemia	28%	14%
Fatigue	24%	2%
Abdominal pain	24%	2%
Headache	20%	2%
Cough	21%	0%
Increased activity of alanine transaminase	17%	7%
Epigastric pain	17%	1%
Neutropenia	19%	14%
Increased activity of aspartate transaminase	14%	3%
Joint pain	15%	1%
Decreased appetite	13%	1%
Constipation	14%	<1%
Dyspnea	14%	3%
Asthenia	12%	1%
Back pain	12%	1%
Vertigo	11%	<1%
Leukopenia	11%	6%
Peripheral edema	10%	<1%
Nasopharyngitis	10%	0%
Limb pain	10%	1%
Pleural effusion	10%	3%

edema, rash, muscle cramps, skin hypopigmentation, and myelosuppression are relatively rare (Table V) [23, 35, 48]. This can be partly explained by low inhibitory activity against c-Kit and PDGFR kinases [25, 34]. In a study by Khoury et al., 20% of patients ($n = 24$) discontinued the treatment due to adverse reactions to bosutinib [42]. In patients treated with bosutinib in the II line of treatment, the treatment was temporarily ceased in 72% of cases, and bosutinib dose was reduced due to adverse events in 49% of cases [44]. The incidence of new adverse events decreased with each successive year of treatment (in the first year – 100%, in the fourth year – 49%) [44]. Discontinuation due to adverse reactions also occurred mainly in the first year of treatment with bosutinib. Some side effects were observed relatively frequently in older patients (i.e. ≥65 years) (fatigue, lack of appetite, weight loss, dyspnoea, pleural effusion) [44].

Gastrointestinal dysfunction

The most frequently observed side effects include gastrointestinal symptoms: diarrhea, nausea and vomiting, and abdominal pain [23, 35, 44]. It is suggested that these symptoms are caused by abnormalities in interstitial cells of Cajal. In clinical trials, diarrhea was observed in 81–86% of patients, and 3/4 grade in 8–9% [35, 42, 48]. Typically, mild diarrhea was observed during the first 4 weeks of treatment. In some cases, it resolved spontaneously after a few days or required the use of symptomatic treatment (such as loperamide). In other cases, it required bosutinib dose reduction (5–6%) or temporary cessation of the treatment (14–15%). Ninety-four percent of patients after re-administration of bosutinib do not experience diarrhea again. Only in 3% of cases ($n = 6$) diarrhea was the reason for the permanent discontinuation of the drug.

Nausea and vomiting were observed in 31–46% of patients, although grade 3/4 was observed only in 1% of patients [35, 42]. They resolved spontaneously or after the antiemetic drugs. Abdominal pain occurred in 15–23% of patients. To reduce the toxic effects of bosutinib on gastrointestinal tract, the drug should be taken with a meal.

Laboratory abnormalities

Increased activity of the transaminases occurred in 14–69% of patients treated with bosutinib in the second and subsequent lines, including 3–30% with grade 3 and 4 [35, 42, 48]. In most cases, the observed abnormalities were transient and required dose reduction or temporary treatment cessation. In 2% of patients it was a cause of permanent treatment cessation. No cases of permanent liver damage were observed. During the first 3 months of bosutinib treatment liver function monitoring is recommended once a month due to the higher incidence of this complication during this period [23, 44]. Other common abnormalities include: hypermagnesemia, hypophosphatemia, and increased activity of lipase [35].

Haematologic toxicity

In phase I/II clinical trials, grade 3/4 anemia, neutropenia, and thrombocytopenia were observed in 8–13%, 17–19%, and

24–25% of patients, respectively [35, 42]. These percentages were higher in patients with CML AP and BP (35%, 41%, and 60%, respectively) [48]. The median time to the onset of myelosuppression was 22 days, and the median duration was 14 days [48]. In the first month of the treatment, compete blood count should be performed weekly [23]. Myelosuppression treatment requires dose reduction or temporary cessation of bosutinib [23].

Other adverse effects

Rash was reported in 44% of patients in the study by Cortes et al., and 22% of patients in the study by Khoury et al. [35, 42]. Pleural effusion was observed in 3% of patients. The most common severe complications in patients in the CML-AP and -BP were pneumonia ($n = 9$) and fever ($n = 6$), respectively [47].

Cardiovascular complications

To determine the cardiovascular safety of bosutinib, treatment results of 570 patients enrolled in I/II phase trials with ≥48 months follow-up were analyzed retrospectively [35, 42, 47, 49]. Exclusion criteria were: drugs prolonging QT interval, clinically significant or uncontrolled heart disease (congestive heart failure, uncontrolled angina pectoris or arterial hypertension within the last 3 months, myocardial infarction within the last 12 months, clinically significant ventricular arrhythmia, diagnosis or suspicion of long QT syndrome, history of long QTc, syncope of unknown etiology), long QTc (mean >0.45 s), irreversible hypomagnesemia or hypokalaemia. The frequency of cardiovascular events related to the treatment was analyzed (number of patients with cardiovascular events to patient-year ratio). The frequency of these events in patients treated with bosutinib in ≥2 line of treatment was low (0.037 for cardiac events and 0.05 for vascular events). Cardiac events were observed in 10.4% of patients, while vascular events in 7.7%. The most frequently reported cardiovascular events were arrhythmias (especially atrial fibrillation), and heart failure. The incidence of new adverse events decreased with treatment duration. In most cases, cardiovascular events were treated pharmacologically and/or bosutinib treatment was ceased. Only 5 patients (0.9%) required permanent cessation of bosutinib therapy. The incidence of vascular side effects of bosutinib is much lower in comparison to nilotinib and ponatinib [50]. ECOG >0 and the history of cardiovascular disease are the main risk factors of cardiovascular adverse events. The risk is further increased by age (>65 years) and hypercholesterolemia.

Cross-intolerance

Cross-intolerance between bosutinib and other TKIs is low and limited mainly to hematological toxicity. In patients who discontinued imatinib treatment due to grade 3/4 adverse reactions, 17% discontinued bosutinib in the second line because of the same side effect, mainly myelosuppression [35, 44]. In a study by Khoury et al., 22% of patients intolerant to dasatinib in II line have experienced the same side effect (myelosuppression) during bosutinib treatment [42]. There was no cross-intolerance regarding grade 3/4 adverse effects in musculoskeletal system, cardiovascular system, digestive tract, respiratory system, and skin.

Indications and dosage

Bosutinib is indicated for the treatment of adult patients with CML in all phases (CP, AP, and BP), who were previously treated with one or more TKI, who cannot be treated with imatinib, nilotinib or dasatinib [23]. Bosutinib is available in oral form in two doses: 100 mg and 500 mg. The recommended daily dose is 500 mg taken with food in order to improve absorption and tolerance. Dose increase to 600 mg daily should be considered in patients who do not achieve CHR after 8 weeks of treatment or CCyR after 12 weeks of treatment and have no grade 3–4 adverse events. Bosutinib is contraindicated in patients with liver failure. There is no need to modify the dose of bosutinib in patients with creatinine clearance ≥25 ml/min.

In moderate or severe, clinically significant, non-hematological toxicity bosutinib should be discontinued. After the symptoms of toxicity resolve, bosutinib can be re-introduced, starting from 400 mg daily. Next, dose increase to 500 mg once daily should be considered [23].

Bosutinib should be temporarily discontinued in patients with over five-fold increase in transaminases activity above the upper limit of normal (ULN). When transaminases activity drops to ≤2.5 × ULN, the treatment should be restarted at 400 mg once daily [23]. In patients with grade 3/4 diarrhea bosutinib should be discontinued. When severity of the diarrhea drops to ≤1, bosutinib treatment can be restarted at 400 mg once daily.

In patients with grade 3/4 neutropenia or thrombocytopenia, bosutinib treatment should be temporarily ceased until neutrophils count increases ≥1000/μl and platelets count is ≥50 000/μl [23]. If cytopenia lasts longer than 2 weeks or re-occurs, bosutinib treatment should be restarted at 100 mg daily after normalization of the parameters.

Summary

Bosutinib (SKI-606) is a potent inhibitor of BCR-ABL kinase and Src family kinases. It is active against the vast majority of mutant BCR-ABL1 resistant to other TKIs, including F317L (resistant to dasatinib) and F359V (resistant to nilotinib), with the exception of T315I (refractory to all TKI with the exception of the ponatinib) and V299L (also resistant to dasatinib) [33, 42].

Toxicity profile of bosutinib differs from other TKIs. These differences may results from minimal activity of bosutinib against c-Kit and PDGFR kinases [25, 34, 36]. The most common side effects include gastrointestinal symptoms (diarrhea, nausea and vomiting, abdominal pain), rash, and increased transaminase activity. In most cases, they appear within the first months of the treatment and disappear spontaneously within a few weeks; however,

some patients may require temporary treatment cessation. There are no irreversible or deadly adverse events, and life-threatening reactions are very rare.

Pleural effusion is less common during bosutinib treatment in comparison to dasatinib: 10% vs 29% (in all toxicity grades) [48, 51]. Unlike nilotinib, bosutinib does not affect cholesterol levels in the blood [23, 52]. Hyperglycemia is less common with bosutinib than nilotinib – 31–41% vs. 50% of patients with all grades and 1–6% vs 6–12% with grade 3/4, respectively [42, 43, 47, 48, 52]. Bosutinib caused significantly less cardiovascular complications than nilotinib, including coronary heart disease (4.2% vs 9.4%), atherosclerosis of the lower limbs (1.4% vs 3.6%), and cerebral ischemia (3.2% vs. 2.3%) [49, 52].

Response rates in patients resistant or intolerant to imatinib treated with bosutinib are similar to the responses observed for dasatinib or nilotinib, although second generation TKIs has never been compared head-to-head [18, 35, 53]. High CHR and CCyR rates were observed in this group of patients [35, 44]. Bosutinib is also effective in the third line treatment of CML-AP i.e. in patients resistant or intolerant to imatinib and other 2nd generation TKIs (dasatinib or nilotinib) [42, 45]. In addition, bosutinib is effective in some patients with CML-AP or -BP after other TKI failure [47].

Second and third line of TKI treatment should be chosen considering the mutation of *BCR-ABL1*, adverse events in the course of TKI treatment and concomitant diseases. One of the main issues in the course of bosutinib treatment are relatively frequent treatment breaks caused by adverse events that may contribute to suboptimal response or resistance development. Considering that diarrhea is one of the main side effects of bosutinib, prophylactic use of anti-diarrheal medication may improve compliance.

In conclusion, bosutinib efficacy in CML patients resistant or intolerant to imatinib or other TKIs is comparable with other 2GTKIs. European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN) recommends bosutinib in the second and subsequent lines of CML treatment. It is a particularly valuable therapeutic option for those patients who cannot be treated with dasatinib or nilotinib because of resistance or intolerance. Bosutinib is the optimal choice for patients with cardio-vascular diseases, hypercholesterolemia or hyperglycaemia (pre-diabetes or diabetes) requiring second or further line of TKI treatment. Considering high incidence of these diseases in the general population, bosutinib is a very important therapeutic option for patient with chronic myeloid leukemia [21, 22].

Authors' contributions/ Wkład autorów

According to order.

Conflict of interest/ Konflikt interesu

Bogdan Ochrem – Pfizer, Novartis, honorarium Speakers Bureau.

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Ethics/ Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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